Alerts, Notices, and Case Reports

California's Public Health Policy on Preventing Neural Tube Defects by Folate Supplementation

GEORGE C. CUNNINGHAM, MD, MPH
Berkeley, California

NEURAL TUBE DEFECTS, which include spina bifida and anencephaly, are among the most common, serious, and costly congenital malformations. About 4 anencephalic and 5 spina bifida births occur per 10,000 births in California. Mortality for anencephaly is almost 100% within the neonatal period. For spina bifida, about a third die in the neonatal period and more than 65% have serious handicaps. The Centers for Disease Control and Prevention (CDC) has estimated lifetime costs at $250,000 per survivor, which calculates as more than $62 million to care for the approximately 250 annual survivors of one California birth cohort.[1]

The CDC has issued a recommendation, based on its review of the literature, that all women at risk of pregnancy receive a daily folate supplement of 0.4 mg.[2] The California Department of Health Services has recently reviewed the available information, and in this alert makes its recommendations.

The evidence that folate can play a role in prevention, although indirect and based on small numbers, is convincing.[3-10] The results reported to date are summarized in Table 1. The various studies evaluating the effects of folate use are difficult to compare.[11,12] Some investigators studied groups that consisted of high-risk mothers of affected children who have a "recurrence" risk estimated at 2% to 5%. Others studied women with no previously affected children who have a lower first "occurrence" risk (0.09% in California).

The studies were also done in groups with different genetic and environmental characteristics because prevalence ranged from 0.09 to 6.0 cases of neural tube defect per 1,000 total births, that is, live births plus fetal deaths.[13-15]

The various studies used different definitions of supplementation based on the time it was started and the length of time it was taken: women took supplements for a varying number of weeks before conception, and supplementation continued for days to months after conception. Studies also varied in the amount of folate ingested daily; some actually studied dietary folate without supplementation. Other epidemiologic differences are also difficult to explain, such as the apparent racial differences in folate effectiveness reported by Mulinare and co-workers.[3]

Most of these studies of occurrence are retrospective and are subject to selection and recall bias. A prospective study done in Hungary reported that 0.8 mg of folate daily could prevent the occurrence of a substantial portion of cases of neural tube defects if given before and during early pregnancy.[9] The data in Hungary, which has a birth prevalence of neural tube defect about three times that in California, were based on a relatively small number of observations.

The best evidence for the prevention of recurrence was the randomized, double-blind, prospective, multicenter placebo study conducted by the Medical Research Council in England.[16] This study conclusively established that about 70% of cases of the expected recurrence could be prevented by 4.0 mg of folate daily taken from the date of entry to the study until 12 weeks after the last menstrual period. This study was done in countries with high prevalence. Based on this study and CDC recommendations,[17] the Department of Health Services advised physicians in California to encourage all women who had a fetus or infant affected or who had a close relative who has had an infant with neural tube defect to take 4.0 mg of folate daily before and during subsequent pregnancies. We have recently modified this recommendation in light of the more recent CDC publication to 0.4 mg a day interconceptionally and 4.0 mg a day periconceptionally.[2]

The cumulative weight of the evidence is that folate supplementation will prevent some cases of neural tube defects from occurring. In California, this could range from 20% to 50%. Therefore, the department endorses the goal of women of childbearing age taking at least 0.4 mg of folate daily. Women who have had a previous affected pregnancy or who have a history of neural tube defect in a close relative should have the level raised to 4.0 mg of folate daily whenever they are attempting to conceive. There is good reason to think that a lower dose, such as 1 mg daily, might be equally effective because studies show that much of the larger dose is lost in the urine.[18] This proposal has not been clinically verified, although there have been reports that taking a daily dose of 0.36 mg of folate substantially reduced recurrence rates.[19,20]

In arriving at this recommendation, we considered those variables that could influence the effectiveness of the folate prevention strategy. The first consideration is whether there is a critical time period for the ingestion of folate relative to the pregnancy. The neural tube forms

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From the Genetic Disease Branch, California Department of Health Services, Berkeley.

Reprint requests to George C. Cunningham, MD, MPH, California Dept of Health Services, 2151 Berkeley Way, Annex 4, Berkeley, CA 94704-1011.

ABBREVIATIONS USED IN TEXT

CDC = Centers for Disease Control and Prevention
FDA = Food and Drug Administration

from the 17th to 19th day after conception and closes by the 28th to the 30th day. When dated by the last menstrual period, closure is complete by a gestational age of about 42 to 44 days or 6.2 weeks. Analysis of folate metabolism indicates that the best measure of adequate folate intake is normal erythrocytic folate because folate stores are built up in the erythrocytes and liver. The serum folate level is only a measure of recent ingestion and can be normal even in a person with depleted folate stores. Only one study reported protection when supplemental folate was given after a positive pregnancy test or missed period.[6] It therefore appears that folate must be given in advance of pregnancy, taken daily, and continued at least for the first six weeks after the last menstrual period.

The next question, the minimum amount of folate needed to ensure protection, is also not clear, but most investigators use 0.4 mg or more per day. This would appear to be a safe dose, but because the metabolic mechanisms involved, including differential absorption, are unknown, some women may need larger amounts. There may be some difference in the bioavailability of dietary folate and supplemental folate tablets.

The department, having endorsed this preventive measure, reviewed the methods of implementation. The possibilities were as follows:

- A program of public education promoting a diet containing sufficient folate;
- The promotion of a folate supplement to be taken by women of childbearing age; and
- Dietary supplementation of cereals or other foods with folate.

The department concluded that dietary fortification was the most effective public health approach and communicated this position to the Food and Drug Administration (FDA).

After some initial misgivings, the FDA has proposed regulation that will permit the use of health claims—that is, prevention of neural tube defect—for foods and vitamin supplements containing sufficient folate and that will require the supplementation of grains and cereal staples with additional folate.[21,22] The department is concerned, however, that the levels of food fortification that the FDA is recommending for folate may be too low to appreciably affect the prevalence of neural tube defect.

In addition to any fortification undertaken, a program of public education as to the importance of adequate folate in the diet should be initiated to ensure that foods naturally high in folate or supplemented with folate will be consumed by women. The department's Women, Infants and Children's Supplemental Food Branch and Maternal and Child Health Branch will be responding to this need. The use of folate tablets or multivitamins containing 0.4 mg of folate should be encouraged if dietary intake is poor. The CDC reports that fewer than 30% of women have 0.4 mg or more of folate in their diets. Folate and folate-containing multivitamins are available on the Medi-Cal formulary. It is important that public education include a caution to women not to attempt to increase folate intake by ingesting excessive vitamin supplements, especially multivitamins. These may contain harmful concentrations of the fat-soluble vitamins, A and D.

We would like to caution against unreasonably high expectations, because defects occur even in women taking supplements. The reduction in birth prevalence of neural tube defect will probably be different from one group to another. The epidemiology and cause for areas of high prevalence are different from those with low prevalence.[23] There is a social gradient in risk and prevalence seen in several countries, but not in some low-prevalence areas. Birth prevalence has declined in areas of high prevalence, but has shown little change in areas of low prevalence. Therefore, the East Coast might have a notable decline in birth prevalence whereas California might well have only a modest decline of 10% to 20%.

Consideration must also be given to the possible adverse consequences of folate supplementation on some women, especially at the 4-mg dose recommended to prevent recurrences. The FDA reviewed this problem

TABLE 1.—*Reported Risk Reduction in Neural Tube Defect (NTD) Occurrence With Folates*

Study	Risk Reduction			Cases of NTD, No.	Controls, No.	Folate Type
	Minimum, %	Average, %	Maximum, %			
Mulinare et al, 1988[3]	34	59	74	347	2,829	Multivitamin supplement
Bower and Stanley, 1989[4]	+21	59	86	77	154	Dietary folate
Mills et al, 1989[5]	+20	0	17	571	573	Multivitamin supplement
Milunsky et al, 1989[6]	17	64	85	49	22,715	Multivitamin supplement
Bower and Stanley, 1992[7]	+109	0	49	23	36	Multivitamin supplement
Martínez-Frías and Rodríguez-Pinilla, 1992[8]	6	31	49	263	7,274	Multivitamin supplement
Czeizel and Dudás, 1992[9]	--	100	--	6	4,704	Multivitamin supplement
Werler et al, 1993[10]	20	60	80	436	3,672	Multivitamin supplement
Total				1,772	41,957	

and conservatively recommended that daily ingestion of folate be kept at 1 mg or less. Some have claimed that folate in sufficiently high dosage, such as 4 mg, can mitigate the effectiveness of some anticonvulsant medication, but there is little evidence to support the concern that a dosage of 0.4 mg daily will have this effect. Patients on valproate therapy need folate supplementation. The possibility should be considered that the megaloblastic anemia resulting from vitamin B_{12} deficiency could be corrected by supplemental folate therapy, whereas progressive neurologic deterioration would not be prevented in the absence of parenteral or oral vitamin B_{12} therapy. This form of anemia is rare in women of childbearing age. It appears, however, that the folate supplementation levels recommended for preventing occurrence, 0.4 mg a day, are unlikely to contribute substantially to this problem. It is not justified to expose pregnancies to the risk of neural tube defect to achieve early diagnosis of this anemia. The risks of higher doses of folate recommended to prevent recurrence must be weighed against the 2% to 5% recurrence risk.

Because in all these studies cases of neural tube defect occur even in women with high levels of folate, pregnant women need to be given the opportunity to be screened, using the California Maternal Serum α-Fetoprotein screening program. In addition, such screening will find abdominal wall defects and cases of Down syndrome that would otherwise go undetected.

Many questions remain unanswered with respect to the relationship of folate to neural tube defects. What is the lowest effective dose? What is the difference between folate-sensitive and folate-resistant cases? Is there an effect on all forms of neural tube defect, such as high defects—above the level of the 12th thoracic vertebra—versus low defects; isolated neural tube defect versus neural tube defect with additional malformations; open versus closed lesions, encephalocele, and the like? Are other nutrients, such as vitamin B_{12}, zinc, or vitamin C, involved in enhancing or inhibiting the preventive effects of folate?

In view of the unanswered questions about what fraction of cases are preventable in California, it is important to the public and clinicians that the department collect data on the occurrence of cases subsequent to folate fortification of foods and widespread folate supplementation. In California, there is mandatory reporting of all cases of neural tube defect diagnosed before 1 year of age. The department collects additional reports from maternal serum α-fetoprotein screening, prenatal diagnostic centers, hospitals, hospital discharge summaries, and fetal and live birth certificates to supplement reporting. The number of cases diagnosed by ultrasonography and terminated without reporting through one of these data collection systems is unknown, however. We encourage all physicians to report these unreported cases, as required by law, to improve the reliability of our evaluating the neural tube defect prevention program. Reporting forms are available on request by calling the Genetic Disease Branch at (510) 540-2534.

The department will continue to monitor this situation and the effectiveness of all prevention efforts as part of its broader goal to prevent birth defects and to improve pregnancy results for all women in California.

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